Remarks

Although an Office Action mailed September 25, 2001 has been received and reviewed, an interview was held on January 16, 2002 in which a supplemental action resetting the time periods was to be sent. Applicants have not received the supplemental action, but are responding to ensure pendency of the instant application. In that regard, a conditional petition for extension of time is set forth hereinafter.

Claims 3, 6, 8, 10, 13, 14, 16, 17, 23-32, 53, 60, 62, 66, 69, 70 and 72-78 are currently pending in the application. Claims 16 and 17 are allowed. Claims 3, 6, 8, 10, 13, 14, 36, 60, 62, 66, 69, 70, 72 and 73 stand rejected. Applicants have canceled claims 23-32, 53, and 74-78. Claims 3, 6, 8, 10, 13, 14, 60, 62, 66, 69, 70, 72 and 73 are amended herein and respectfully request their reconsideration. All claim amendments and cancellations are made without prejudice or disclaimer.

1. Examiner Interview

Applicants wish to thank the Examiner for the courtesy extended during the personal interview conducted January 16, 2002. The applicants found this interview especially productive as evidenced by the Interview Summary (Paper No. 18),

> [a]pplicants were advised that a supplemental action would be sent (taking into account the amendment filed September 10, 2001). Applicants proposed claim amendments which should obviate the outstanding rejections.

Applicants have amended the claims herein consistent with the discussions at the interview.

2. Sequence Listing

Applicants note with appreciation that the Sequence Listing filed July 2, 2001 is acceptable and has been entered in this application.

3. 35 U.S.C. § 112 Rejections

Claims 13 and 69 were rejected in the Office Action under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Deposit Declaration with Applicant's earlier amendment was rejected in the Office Action as allegedly deficient for failure to comply with 37 C.F.R. § 1.804(b).

On January 28, 2002, applicants submitted a replacement Deposit Declaration to remedy any deficiency and believe no further action is required on this issue.

Claims 3, 8, 10, 14, 60, 62, 66, 69, 70, 72 and 73 stand rejected in the Office Action as assertedly being indefinite under 35 U.S.C. § 112, second paragraph.

Claims 62, 66, 69, 70, 72 and 73 were rejected as assertedly being vague with respect to the term "essentially only one" homologous recombination event. Applicants have amended these claims to remove this term and recite that the overlapping sequences in the two nucleic acids of those claims each include essentially only one continuous sequence such that homologous recombination may occur. Applicants respectfully submit that no further action is required on this issue and request these claims be allowed.

Claims 3, 10 and 73 were rejected as assertedly being vague with respect to the phrase "derivatives and/or analogues thereof...." Applicants respectfully disagree with this assertion for the reasons stated in the prior amendment, but have amended these claims to remove this term for the purpose of expediting allowance of this application. Applicants respectfully submit that these claims are definite and supported by the specification and requests they be allowed.

Claim 14 was rejected as assertedly being vague in the Office Action with respect to the term "said nucleic acid" in line 6. Claim 14 as amended herein now recites "said physically linked nucleic acid" at line 6, antecedent basis for which is provided in claim 14. Applicants respectfully submit that claim 14 is now definite and request withdrawal of the rejection.

Claims 8, 60 and 73 were rejected as being vague for depending from a cancelled claim. Claims 8 and 60 have been amended to stand independently. Claim 8 incorporates the terms of canceled claim 1 from which it depended and claim 60 incorporates the terms of canceled claim 2 from which it depended. Applicants respectfully submit that claim 73 is an independent claim, and request it be allowed.

4. 35 U.S.C. § 102 Rejections

Claims 3, 6, 14, 62 and 70 stand rejected in the Office Action as allegedly anticipated by Berkner, K.L., Expression of Heterologous Sequences in Adenoviral Vectors, Curr. Top. Micro. Immuno., Vol. 158, pp. 39-66, 1992 ("Berkner") and Stratford-Perricaudet, L. et al., Gene Transfer

Into Animals: The Promise of Adenovirus, Human Gene Transfer, Vol. 219, pp. 51-61, 1991 ("Stratford-Perricaudet"). Applicants respectfully submit that these amended claims define over the cited references for at least the reasons discussed further herein.

As discussed in the interview, each of amended claims 3, 6, 14, 62 and 70 are directed to forming adenoviral vectors by welding together two nucleic acids in a cell. The two nucleic acids include partially overlapping sequences and other elements. Each claim now includes the element that the nucleic acids present in the cell do not include sequence overlap leading to the formation of replication competent adenovirus. Support for this element may be found in the specification at many locations, including: page 22, line 8 to page 23, line 22; page 29, lines 13-16; page 36, line 14 to page 37, line 5; page 41 lines 4 to 6; page 48, line 22 to page 49, line 2; the number of methods and systems including this element discussed from pages 55 line 14 to page 60, line 15; and Example 2, Plasmid based system for rapid RCA-free generation of recombinant adenoviral vectors from page 75, line 27 to page 90, line 72. The inclusion of this element overcomes the problem of generating replication competent adenovirus while producing recombinant adenoviral vectors, which is common in the prior art as discussed at page 10, line 28 to page 11 line 2 and page 12 lines 8-12 of the specification. This element and the advantage provided thereby are not disclosed in either the Berkner or the Stratford-Perricaudet references. Applicants thus respectfully submit that amended claims 3, 6, 14, 62 and 70 are not anticipated by those references, as they include elements not found in the cited references, and applicants accordingly request these claims be allowed.

5. 35 U.S.C. § 103 Rejections

Claims 13 and 69 stand rejected under 35 U.S.C. § 103(a) as being obvious over Berkner or Stratford-Perricaudet in view of U.S. Patent 5,994,128 to Fallaux et al. ("Fallaux").

As discussed at the interview, amended claims 13 and 69 now each include the element that the nucleic acids present in the cell do not include sequence overlap leading to the formation of replication competent adenovirus. As discussed in the preceding section, Berkner and Stratford-Perricaudet fail to teach this claim element. A system or method created by combining the teachings of those references with the Fallaux reference would similarly lack this element. Mere substitution of the PER.C6 cell line for the 293 cells used in the Berkner and Stratford-Perricaudet references

would not result in this element. The plasmids disclosed in the Berkner and Stratford-Perricaudet references contain overlaps that would result in the generation of replication competent adenovirus, even were such a substitution made.

Further, Berkner suggests different methods for reducing the production of replication competent adenovirus during the generation of recombinant adenoviral vectors, including the use of conditionally defective vectors and subgenomic Ad plasmid DNA fragments. Applicants respectfully submit one skilled in the art would be motivated to reduce the replication competent adenovirus produced using the Berkner nucleic acid sequences using such methods, rather than substitute an alternative packaging cell line that would not reduce such unwanted adenovirus production when used in connection with the Berkner nucleic acid sequences.

For the foregoing reasons, applicants respectfully submit this rejection should be withdrawn and amended claims 13 and 69 be allowed.

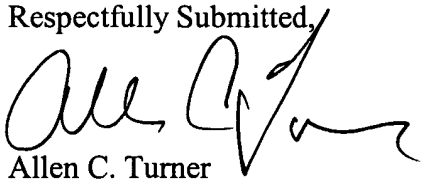
6. Conditional Request for Extension of Time:

If applicants' understanding that a Supplemental Action would issue re-starting the time period for responding to the September 25, 2002 office action was mistaken, applicants hereby petition the Office for a three month extension of time under 37 C.F.R. § 1.136(a). Any fees thus required may be charged to Deposit Account No. 20-1469.

Conclusion

Claims 16 and 17 are currently allowed and amended claims 3, 6, 8, 10, 13, 14, 60, 62, 66, 69, 70, 72 and 73 are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. Should the Office determine that additional issues remain which might be resolved by a telephone conference, he is respectfully invited to contact Applicant's undersigned attorney.

Respectfully Submitted,



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Date: March 18, 2002

Enclosures: Version of Amendments with Markings to Show Changes Made
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

3. (Amended three times) A method for generating an adenoviral vector comprising welding together two nucleic acid molecules in a cell wherein both nucleic acid molecule of said two nucleic acid molecules comprise only one adenovirus inverted terminal repeat or a part[, derivative, and/or analogue] thereof having the function of an inverted terminal repeat, said two nucleic acid molecules further comprising partially overlapping sequences capable of combining with one another allowing the generation of a physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal and a nucleic acid sequence of interest or functional parts thereof, wherein the two nucleic acid molecules present in the cell do not include sequence overlap leading to the formation of replication competent adenovirus.

6. (Amended three times) A method for generating an adenoviral vector comprising welding together [in a mammalian cell] two nucleic acid molecules in a mammalian cell wherein said two nucleic acid molecules comprise partially overlapping sequences capable of combining with one another allowing the generation of a physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal and a nucleic acid sequence of interest or functional parts thereof; wherein said two nucleic acid molecules are not capable of replicating in said mammalian cell prior to said welding together, and wherein the two nucleic acid molecules present in the mammalian cell do not include sequence overlap leading to the formation of replication competent adenovirus.

8. (Twice amended) A method [according to claim 1,] for generating an adenoviral vector comprising welding together two nucleic acid molecules in a cell, wherein said two nucleic acid molecules comprise partially overlapping sequences capable of combining with one another allowing the generation of a physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal and a nucleic acid of interest or functional parts thereof and wherein at least one nucleic acid molecule of said two nucleic acid

molecules provided to said cell comprises an adenovirus inverted terminal repeat which, on one side, is essentially free of other nucleic acid.

10. (Twice amended) A method for generating an adenoviral vector comprising welding together two nucleic acid molecules wherein said two nucleic acid molecules comprise partially overlapping sequences capable of combining with one another allowing the generation of a physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal and a nucleic acid sequence of interest or functional parts[, derivatives and/or analogues] thereof[;], wherein at least one nucleic acid molecule of said two nucleic acid molecules comprises an adenovirus inverted terminal repeat made essentially free of other nucleic acid on one side using a restriction enzyme that acts on a site which is not present in adenoviral vector nucleic acid in said at least one nucleic acid molecule.

13. (Three times amended) A method for generating an adenoviral vector comprising welding together[;], in a PER.C6 cell (ECACC 96022940), two nucleic acid molecules wherein said two nucleic acid molecules comprise partially overlapping sequences capable of combining with one another allowing the generation of a physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal and a nucleic acid sequence of interest or functional parts thereof, and wherein the two nucleic acid molecules present in the cell do not include sequence overlap leading to the formation of replication competent adenovirus.

14. (Three times amended) A method for generating an adenoviral vector comprising welding together, in a cell, two nucleic acid molecules wherein said two nucleic acid molecules comprise partially overlapping sequences capable of combining with one another allowing the generation of a physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal and nucleic acid sequence of interest or functional parts thereof; said physically linked nucleic acid in said cell further comprising a nucleic acid sequence encoding an adenoviral E2-region and/or an adenoviral E4-region protein, and wherein the

two nucleic acid molecules present in the cell do not include sequence overlap leading to the formation of replication competent adenovirus.

60. (Amended) A method [according to claim 2,] for generating an adenoviral vector comprising welding together, through homologous recombination, two nucleic acid molecules comprising partially overlapping sequences wherein said overlapping sequences of each nucleic acid molecule of said two nucleic acid molecules comprise essentially only one continuous sequence such that homologous recombination may occur leading to the generation of physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal and a nucleic acid of interest or functional part thereof, wherein said welding together is performed in a cell or a functional part thereof.

62. (Twice amended) A method for generating an adenoviral vector comprising welding together, through homologous recombination in a mammalian cell, two nucleic acid molecules incapable of replicating in said mammalian cell prior to said welding together; said two nucleic acid molecules comprising partially overlapping sequences wherein said overlapping sequences [allow essentially only one homologous recombination which leads] on each nucleic acid molecule of said two nucleic acid molecules comprise essentially only one continuous sequence such that homologous recombination may occur, leading to the generation of a physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal and a nucleic acid sequence of interest or functional parts thereof, and wherein the two nucleic acid molecules present in the cell do not include sequence overlap leading to the formation of replication competent adenovirus.

66. (Twice amended) A method for generating an adenoviral vector comprising welding together, through homologous recombination, two nucleic acid molecules comprising partially overlapping sequences wherein said overlapping sequences [allow essentially only one homologous recombination which leads] of each nucleic acid molecule of said two nucleic acid molecules comprise essentially only one continuous sequence such that homologous recombination may occur,

leading to the generation of a physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal and a nucleic acid sequence of interest or functional parts thereof[;], at least one nucleic acid molecule of said two nucleic acid molecules provided to said cell comprises an adenovirus inverted terminal repeat which, on one side, is made essentially free of other nucleic acid [on one side] using a restriction enzyme that acts on a site which is not present in adenoviral vector nucleic acid in said at least one nucleic acid molecule.

69. (Twice amended) A method for generating an adenoviral vector comprising welding together, through homologous recombination in a PER.C6 cell (ECACC 96022940), two nucleic acid molecules comprising partially overlapping sequences wherein said overlapping sequences [allow essentially only one homologous recombination which leads] of each nucleic acid molecule comprise essentially only one continuous sequence such that homologous recombination may occur, leading to the generation of a physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal and a nucleic acid sequence of interest or functional parts thereof, and wherein the two nucleic acids present in the cell do not include sequence overlap leading to the formation of replication competent adenovirus.

70. (Twice amended) A method for generating an adenoviral vector comprising welding together, through homologous recombination, two nucleic acid molecules comprising partially overlapping sequences wherein said overlapping sequences [allow essentially only one homologous recombination which leads] of each nucleic acid molecule of said two nucleic acid molecules comprise essentially only one continuous sequence such that homologous recombination may occur, leading to the generation of a physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal and a nucleic acid sequence of interest or functional parts thereof; said physically linked nucleic acid further comprising a nucleic acid sequence encoding an adenoviral E2-region and/or an adenoviral E4-region protein, and wherein the two nucleic acids present in the cell do not include sequence overlap leading to the formation of replication competent adenovirus.

72. (Twice amended) A method for generating an adenoviral vector comprising welding together, through homologous recombination, two nucleic acid molecules comprising partially overlapping sequences wherein said overlapping sequences [allow essentially only one homologous recombination which leads] of each nucleic acid molecule of said two nucleic acid molecules comprise essentially only one continuous sequence such that homologous recombination may occur, leading to the generation of a physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal and a nucleic acid sequence of interest or functional parts thereof; at least one nucleic acid molecule of said two nucleic acid molecules comprising an adenoviral capsid protein encoding nucleic acid derived from two different adenovirus serotypes.

73. (Twice amended) A method for generating an adenoviral vector comprising welding together through homologous recombination, two nucleic acid molecules comprising partially overlapping sequences wherein said overlapping sequences [allow essentially only one homologous recombination which leads] of each nucleic acid molecule of said two nucleic acid molecules comprise essentially only one continuous sequence whereby homologous recombination may occur, leading to the generation of a physically linked nucleic acid comprising at least two functional adenovirus inverted terminal repeats, a functional encapsulation signal, a nucleic acid encoding at least one adenoviral E1-region protein, at least one adenoviral E2-region encoded protein and/or at least one adenoviral E4-region encoded protein and a nucleic acid sequence of interest or functional parts thereof and wherein at least one of said E1-region encoded proteins is under transcriptional control of a conditionally active promoter.